Pulmonary Hypertension

Respiratory Critical Care Conference, September 2016

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University of Washington School of Medicine
Take home points

1. Pulmonary hypertension is not one disease but many
   Appropriate treatment requires appropriate diagnosis

2. Treatment for pulmonary arterial hypertension is focused on diuresis and afterload reduction
   The current proliferation of drugs for PAH leaves many unanswered questions but a structured goal-directed approach is possible

3. There has been progress in pulmonary arterial hypertension, but there is more work to be done
   Novel targets and approaches are needed
The spectrum of diseases with high pulmonary pressures
The Physiology

\[ mPAP = PVR \times CO + PCWP \]

- \( mPAP \): mean pulmonary artery pressure;
- \( PCWP \): pulmonary capillary wedge pressure;
- \( PVR \): pulmonary vascular resistance;
- \( CO \): cardiac output.
A violet by any other name... still isn’t a rose

- High pressure
- Primary versus Secondary
- WHO Classification Scheme
### Pulmonary hypertension heterogeneity

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Pulmonary Arterial Htn</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>•</strong> Idiopathic, heritable, toxic,</td>
<td></td>
</tr>
<tr>
<td><strong>•</strong> Associated (HIV, CREST, etc)</td>
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<table>
<thead>
<tr>
<th>Group 2</th>
<th>Left Heart Disease</th>
</tr>
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<tbody>
<tr>
<td><strong>•</strong> Systolic, diastolic, valvular</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Group 3</th>
<th>Alveolar Hypoxia/Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>•</strong> Hypoxemia: Sleep Disorders</td>
<td></td>
</tr>
<tr>
<td><strong>•</strong> Capillary Bed Loss: ILD/COPD</td>
<td></td>
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<thead>
<tr>
<th>Group 4</th>
<th>Thromboembolic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>•</strong> CTEPH, Tumor embolism</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 5</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>•</strong> Sarcoid, LAM, Vasculitis,</td>
<td></td>
</tr>
<tr>
<td><strong>•</strong> metabolic disease</td>
<td></td>
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</tbody>
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WHO Group 1 – Pulmonary Arterial Hypertension

Endothelial thickening

Plexiform lesions & smooth muscle hypertrophy

In situ thrombosis

Zwicke DL. Advances in Pulmonary Hypertension (2011)
WHO Group 2 – Pulmonary Venous Hypertension

- Increased wall stress
- Activation of vascular stretch receptors

Decreased pulmonary vascular compliance

WHO Group 2

Mitral or VSD intervention

- VSD closure
- Mitral valve surgery

LVAD placement

Wedge Pressure (mmHg)

PVR (wood units)

WHO Group 3 – Parenchymal Lung Disease & Hypoxia

Normal lung

Pulmonary Fibrosis

Schematic of emphysema

Emphysema
WHO Group 5 – Miscellaneous
Causes of pulmonary hypertension

- Left heart disease, 67.9%
- Unknown, 15.4%
- PAH, 2.7%
- CTEPH, 0.6%
- Lung disease/sleep-related hypoventilation, 9.7%
- Misc., 2.7%

Natural History and Evaluation of WHO Group 1-Pulmonary Arterial Hypertension
## Symptoms at Diagnosis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Initial Symptom (%)</th>
<th>At Diagnosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>60</td>
<td>98</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
<td>73</td>
</tr>
<tr>
<td>Angina*</td>
<td>7</td>
<td>47</td>
</tr>
<tr>
<td>Near Syncope</td>
<td>5</td>
<td>41</td>
</tr>
<tr>
<td>Syncope*</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>Leg Edema*</td>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>Palpitations</td>
<td>5</td>
<td>33</td>
</tr>
</tbody>
</table>

* = symptoms of advanced disease, also includes dyspnea at rest

## Delays in diagnosis?

<table>
<thead>
<tr>
<th>Historical Epoch</th>
<th>Time from 1\textsuperscript{st} Symptom to diagnosis</th>
</tr>
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<tbody>
<tr>
<td>Kennedy Era</td>
<td>~1.8 years</td>
</tr>
<tr>
<td>Reagan Era</td>
<td>~1.3 years</td>
</tr>
<tr>
<td>Bush Era</td>
<td>~1.1 years</td>
</tr>
</tbody>
</table>
EKG is abnormal in ~ 80% of patients at dx

Big RA: P-wave >2 boxes high in II

RVH: R-wave >7 boxes in V1 (with right axis and ‘large’ S-waves in v5/6)

Right Heart Strain: Flipped lateral leads and ↓ ST

CXR is abnormal in ~ 90% of patients at dx
Chest CT

PA/Ao Diameter >1 to identify PH

- Sensitivity 0.70
- Specificity 0.92

Echo

- Sensitivity 0.76
- Specificity 0.58

Systolic PAP of 40mmHg on echo to identify PAH

Janda S et al. Heart doi:10.1136/hrt.2010.212084
Right heart catheterization

Absolutely needed before you make the diagnosis and start therapy

After you make the diagnosis the following tests if not already done should all be considered on the merits to treat the disease appropriately:

Chest CT, PFTs, Echocardiogram, VQ Scan, ANA, RF, anti-ccp, ANCA, anti-scl70, anti-ro, anti-la, anti-ds dna, HIV, toxicology screen, a history, Liver function tests, sleep study, ova and parasites, schistosomiasis serology
Natural History: PAH

- **NYHA** stages:
  - I
  - II
  - III
  - IV

- **PAP** (Pulmonary Arterial Pressure)
- **PVR** (Pulmonary Vascular Resistance)
- **CO** (Cardiac Output)
- **BNP** (Brain Natriuretic Peptide)

Over time (X-axis), CO and NYHA stage increase while PAP and PVR decrease.
Treatment for WHO Group 1-Pulmonary Arterial Hypertension
The “Big 3” Pathways in PAH

Research progress

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td>Historical Controls</td>
<td>68%</td>
</tr>
<tr>
<td>Bosentan</td>
<td>~90%</td>
</tr>
<tr>
<td>Flolan/Remodulin</td>
<td>~85%</td>
</tr>
</tbody>
</table>

How and when to treat

Treatment naive patient

PAH confirmed by expert center

General measures
Supportive therapy

Acute vasoreactivity test (I-PAH, H-PAH, D-PAH only)

Vasoreactive

CCB Therapy

Non-vasoreactive (or not IPAH/HPAH/DPAH)

Low Risk

Oral Monotherapy

Oral Combo Therapy

Inadequate response

Double/triple sequential therapy OR lung transplant

High Risk

Parenteral Therapy
Supportive therapy & General Measures!

“In most but not all cases RV failure (in PAH) is associated with fluid overload and a negative fluid balance is a key to successful therapy.” – Marius Hoeper

- Approach chronic right heart failure conceptually like left heart failure (BNP, diuresis, salt avoidance, etc)
- Oxygen for sitting or ambulatory saturation <88%
- Evaluate and treat for sleep apnea
- Evaluate and treat for thyroid dysfunction
- Don’t get pregnant!
- Exercise
- Eat right (and treat iron deficiency aggressively – ferritin goal >100)

Hoeper et al, AJRCCM, 184: 1114-24, 2011
A note on diuretics

Some evidence that furosemide isn’t the best choice....

Meta-analyses of unblinded but randomized evidence in 471 participants with torsemide relative to furosemide:

RR for heart failure readmission: 0.41 (p<0.01)
RR for mortality: 0.86 (p=0.54)

* non-randomized evidence is all over the place
** Loop diuretic is typically paired with spironolactone based on an observational re-analysis of the ambrisentan trials

DiNicolantonio et al, Future Cardiol, 8: 2012, Maron BA et al, Am J Cardiol, 112: 2013
Exercise in PAH... Is it safe? effective?

Safety:

In over 700 participants the only significant side effects in cardiac rehabilitation were dizziness.

Efficacy:

Six Minute Walk Distance: Mean improvement 72m
Peak VO₂: mean improvement 1.1 – 2.1 mL/kg/min
NYHA Functional Class: ~1 NYHA class improvement

Even some evidence that exercise decreases resting PVR (~2 wood units !@#)

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General measures

Supportive therapy

Galie N, ESC/ERS 2015 Guidelines
# Risk Strata

<table>
<thead>
<tr>
<th>Estimated one-year mortality</th>
<th>Low Risk (&lt;5%)</th>
<th>Intermediate (5-10%)</th>
<th>High Risk (&gt;10%)</th>
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</thead>
<tbody>
<tr>
<td>Right heart failure</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional</td>
<td>Repeated</td>
</tr>
<tr>
<td>WHO/NYHA Functional Class</td>
<td>I or II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>CPET</td>
<td>VO₂ max &gt;15</td>
<td>VO₂ max 11-15</td>
<td>VO₂ max &lt;11</td>
</tr>
<tr>
<td></td>
<td>Ve/VCO₂ &lt;36</td>
<td>Ve/VCO₂ 36-45</td>
<td>Ve/VCO₂ &gt;45</td>
</tr>
<tr>
<td>BNP</td>
<td>&lt;50</td>
<td>50-300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RA &lt;8 mmHg</td>
<td>RA 8-14 mmHg</td>
<td>RA &gt;14 mmHg</td>
</tr>
<tr>
<td></td>
<td>CI &gt;2.5</td>
<td>CI 2.0-2.4</td>
<td>CI &lt;2</td>
</tr>
<tr>
<td></td>
<td>SvO₂ &gt;65%</td>
<td>SvO₂ 60-65%</td>
<td>SvO₂ &lt;60%</td>
</tr>
</tbody>
</table>

Galie N, ESC/ERS 2015 Guidelines
Nitric oxide targeted therapy

Sildenafil, tadalafil, and riociguat

- Quickest action of the pulmonary vasodilators (hours to days)
- Side effects (headaches, myalgias, etc) are common, but typically subside in a few weeks
- Should NEVER be used together or alongside nitrates
- *May* have some benefit in WHO Group II Pulmonary hypertension
- Biggest impact on systemic vascular resistance (especially riociguat) and should be used cautiously in Eisenmenger’s, Cirrhosis, etc.
- Riociguat is the only approved medical therapy for CTEPH
Endothelin Receptor Antagonists

Bosentan, Ambrisentan, Macitentan

- Differ in dosing frequency and side effects
- Can take several weeks to begin seeing an effect
- No data on comparative efficacy, but some combinations may interact (e.g. bosentan + sildenafil may interact and ambrisentan + tadalafil have been studied together directly)
- Bosentan is rarely used because of the need for monthly LFT testing and the risk for idiosyncratic liver injury
Prostacyclin-targeted therapy

Treprostinil (SQ, IV, inhaled, PO), Epoprostenol (IV), Selexipag (PO)

- Continuous parenteral NOT equivalent to oral or inhaled and not appropriate for all patients
- Can take several weeks to begin seeing an effect and are weak negative inotropes (e.g. rough for salvage therapy in a decompensated ICU patient)
- Be attentive for stigmata of overdosing (hypotension, flushing, jaw pain, myalgia, low back pain, diarrhea) or underdosing (dyspnea, tachycardia, lightheadedness, cardiorenal syndromes, etc)
- “Weight-based” parenteral dosing, but fixed at the initial weight when the med was started
Acute management in PAH patients

- Identify and treat triggering factors
- Optimize fluid balance
- Reduce RV afterload
- Optimize cardiac output
- Optimize perfusion pressure

Adapted from Hoeper et al, AJRCCM, 184: 1114-24, 2011
Identify and Treat Triggering Factors

As with left heart failure, look for common problems that are derangements of sudden change that can be fixed

- Infection, Infection, Infection!
- Missed medications
- Dietary indiscretion
- Bleeds/Anemia
- Atrial Fibrillation
- Myocardial infarction
- Pulmonary embolism

Hoeper et al, AJRCCM, 184: 1114-24, 2011
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2. Treatment for pulmonary arterial hypertension is focused on diuresis and afterload reduction
   *The current proliferation of drugs for PAH leaves many unanswered questions but a structured goal-directed approach is possible*

3. There has been progress in pulmonary arterial hypertension, but there is more work to be done
   *Novel targets and approaches are needed*
Thank you!

Pulmonary Vascular Disease Clinic

David Ralph, MD & Stephanie Harris-Nolley, RN BSN

Thank you to the patients and families who contributed to the work described in this presentation

Please feel free to e-mail learyp@uw.edu with any non-urgent questions

www.phassociation.org online university has good clinical resources and patient support
Appendix

• Ventricular interdependence
• Vasodilators for left heart failure
• Comorbidity
Ventricular Interdependence
“The Reverse Bernheim Effect”

• Pressure is typically less than 25 mmHg and PVR >8wu in the rare case of ventricular interdependence

• “PAH” patients with high wedge on subsequent caths have less treatment response to pulmonary vasodilators and may not be PAH but unmasked HFpEF

Frost A, Chest (2013); & Wain Hobson, IJC Heart & Vessels (2014)
Non-Group I: Therapy doesn’t work

WHO Group II Pulmonary Hypertension- HFrEF

*Endothlin-receptor antagonists*

REACH-1, EARTH, ENABLE: no benefit

*Prostacyclin analogues (epoprostenol)*

FIRST: stopped early for excess heart failure

Non-Group I: Therapy doesn’t work

WHO Group II Pulmonary Hypertension- HFpEF

*Endothlin-receptor antagonists*

Sitaxsentan: 90s longer on the treadmill but no difference in LV mass, diastology or NYHA FC at 24 weeks

Non-Group I: Exceptions to the rule

Groups and treatments where therapy might work....

Left heart failure: sildenafil or riociguat
- EF <40%, RCT of sildenafil (n=34) increased HRQOL and exercise capacity
- EF<40%, RCT of sildenafil (n=55) improved: EF, E’ E/E’, left atrial volume index and LV mass index
- EF >50%, RCT of sildenafil (n=216)/RELAX trial: no difference
- EF >50%, RCT of sildenafil (n=44) with hemodynamics and elevated TPG: reduced lung water, PCWP, PA pressures, etc at 12 months
- EF >50%, Riociguat (n=21) improved stroke volume

Non-operative chronic thromboembolic pulmonary hypertension

Comorbidity Management- Bleeding

Bleeding

- Beware volume overload with PRBC transfusion and consider diuresis with each unit

- Platelets and FFP both of which have high concentrations of thomboxane A2 (a pulmonary vasoconstrictor) may lead to profound pulmonary vasoconstriction

Comorbidity Management- PE

- Thrombolysis should be considered if no contraindications

- The MOPETT Trial suggests improved hemodynamics with no significant bleeding if ½ dose TPA is used (e.g. 50mg if weight is over 50kg with 10mg pushed over the first minute and 40mg infused over 2 hours)

Comorbidity Management - Ventilation

- **TRY NOT TO INTUBATE!**

- **If you do intubate:**
  
  - **PVR may be lowest at functional residual capacity**
    - Therefore, *low tidal volume ventilation may be appropriate* for all patients with PAH
  
  - **The rest of the ARDS playbook may not be as good**
    - PEEP increases PVR and should be minimized
    - Permissive hypercapnia can increase PVR by more than 50% and mPAP by more than 30%